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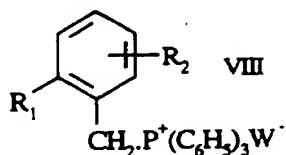
Process a) may be performed following standard procedures for hydrogenation of double or triple bonds, preferably using hydrogen in combination with hydrogenation catalysts, such as Pd, Pt or Rh, most preferably Pd on charcoal and, for reducing a Schiff-base (formula IIc) using a complex metal hydride, such as sodium cyanoborohydride, in an inert solvent, e.g. an alcohol.

Process b) is performed according to standard reactions for the synthesis of heterocycles fused to a benzene ring starting from appropriately substituted benzene derivatives.

Process c) is performed according to standard procedures for O- and N-alkylation using benzyl halogenides, -sulfates or -mesylates, preferably benzylbromides, in the presence of a suitable base, preferably alkali carbonates or alkali hydrides, in an inert and preferably polar solvent, such as acetone or dimethylformamide, at temperatures between -20 and 120° C, preferably between room temperature and 60° C.

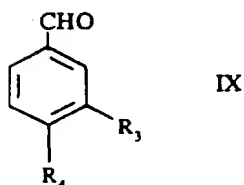
Process d) is performed according to standard procedures for the coupling of vinylstannanes (Stille coupling) or vinylboranes, preferably prepared by addition of boronhydrides to alkynes of formula VIIIb with arylhalogenides, preferably aryl iodides and aryl bromides, under transition metal catalysis, preferably using palladium catalysts.

The starting material of formula IIa may be prepared reacting a compound of formula

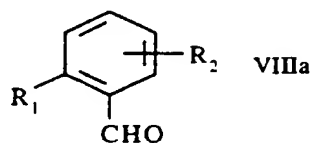


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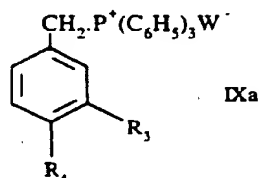
with a compound of formula



or reacting a compound of formula

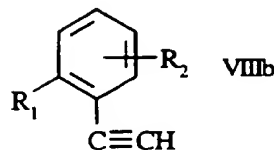


with a compound of formula

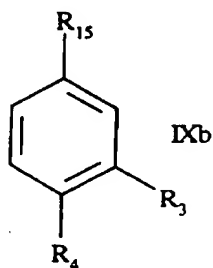


wherein the substituents are as defined above and  $W^-$  represents an anion, preferably bromide. This process may be carried out in a manner conventional for Wittig/Horner/Emmons type reactions by treatment of the phosphor component with a base, such as an alkyl lithium, an alkali hydride or an alkali amide, e.g. sodium amide, lithium diisopropylamide, or an alkali alcoholate, at a temperature between  $-70^\circ\text{C}$  and  $100^\circ\text{C}$  and simultaneous or subsequent conversion with the carbonyl component at temperatures between  $-70^\circ$  and  $120^\circ\text{C}$ , preferably  $-60^\circ$  to  $60^\circ\text{C}$ , in appropriate solvents, such as, for example, tetrahydrofuran, toluene or dimethylsulfoxide.

The starting material of formula IIb may be prepared reacting a compound of formula



with a compound of formula



wherein the substituents are as defined above and  $R_{15}$  represents halogen, preferably iodine, following standard procedures for the Heck reaction of haloolefines with acetylenes.

The starting compounds of formula III can be prepared analogously as described for the compounds of formula I.

The other starting materials and intermediate compounds are either known or can be prepared according to known methods or analogously as described in the examples.

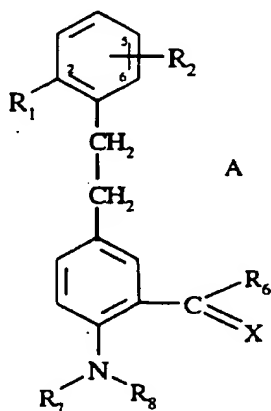
In the following examples, which illustrate the invention but in no way limit its scope, references to temperature are in degrees celsius.

**Example 1: 5-[2-(2,5-Dimethoxyphenyl)ethenyl]-2-acetylamino benzoic acid methyl ester (process a)**

150 mg of 5-[2-(2,5-dimethoxyphenyl)ethenyl]-2-acetylamino benzoic acid methylester are dissolved in 10 ml of ethyl acetate. After addition of 25 mg of palladium (10% on charcoal) the mixture is stirred overnight under an atmosphere of hydrogen and filtered over celite. The filtrate is evaporated in vacuo to obtain the title compound as colourless crystals.

mp: 81-83°.

Analogously as described in example 1 the following compounds of formula A



are obtained:

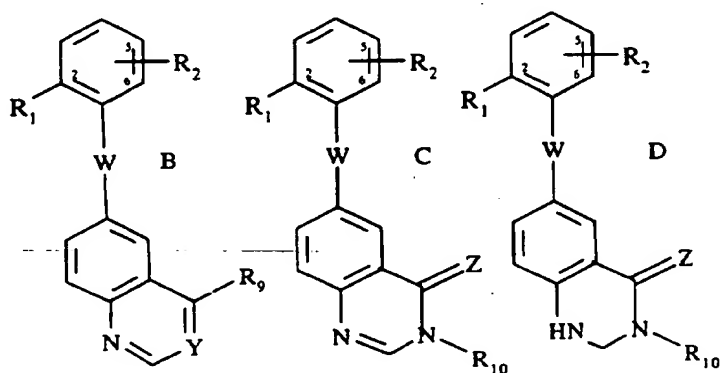
Ex.:	R <sub>1</sub>	R <sub>2</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	X	m.p.:
2	OCH <sub>3</sub>	5-OCH <sub>3</sub>	O-nBu	Ac	H	O	58°
3	-	6-OCH <sub>3</sub>	OCH <sub>3</sub>	Ac	H	O	108°
4	-	5-OCH <sub>3</sub>	CH <sub>3</sub>	H	H	O	oil
5	-	-	NH <sub>2</sub>	H	H	O	112°

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**Exempl 6: 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethyl-quinazoline**  
(process a)

150 mg of 6-[2-(2,5-dimethoxyphenyl)ethynyl]-4-ethyl-quinazoline are dissolved in 10 ml of ethyl acetate. After addition of 20 mg of palladium (10% on charcoal) the mixture is stirred overnight under an atmosphere of hydrogen and subsequently filtered over celite. The filtrate is evaporated in vacuo and the residue crystallised from cyclohexane to obtain the title compound as colourless crystals. mp: 74°.

Analogously as described in example 6 the following compounds of formula B, C and D



are obtained:

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Ex:	form	W	R <sub>1</sub>	R <sub>2</sub>	Y	R <sub>9</sub>	Z	R <sub>10</sub>	m.p.:
7	C	-CH <sub>2</sub> CH <sub>2</sub> -	OCH <sub>3</sub>	5-OCH <sub>3</sub>	-	-	O	H	157°
8	B	-"	-"	-"	N	OC <sub>2</sub> H <sub>5</sub>	-	-	80°
9	B	-"	-"	-"	N	NAC <sub>2</sub>	-	-	118°
10	B	-"	-"	6-OCH <sub>3</sub>	N	OCH <sub>3</sub>	-	-	133-135°
11	C	-"	-"	-"	-	-	O	H	198-201°
12	B	-"	OH	5-OCH <sub>3</sub>	N	OCH <sub>3</sub>	-	-	176-180°
13	B	-"	OCH <sub>3</sub>	-"	N	NHCH <sub>3</sub>	-	-	147-150°
14	B	-"	-"	5-OH	N	OCH <sub>3</sub>	-	-	174-176°
15	B	-"	-"	5-OCH <sub>3</sub>	N	H	-	-	78-80°
16	B	-"	-"	-"	N	OCH <sub>3</sub>	-	-	62°
17	B	-"	-"	-"	N	CH <sub>3</sub>	-	-	70°
18	B	-"	OC <sub>2</sub> H <sub>5</sub>	5-OC <sub>2</sub> H <sub>5</sub>	N	C <sub>2</sub> H <sub>5</sub>	-	-	80°
19	B	-"	C <sub>2</sub> H <sub>5</sub>	5-C <sub>2</sub> H <sub>5</sub>	N	-"	-	-	42°
20	B	-"	OCH <sub>3</sub>	6-OCH <sub>3</sub>	N	-"	-	-	104-108°

**Example 21: 6-(2,5-Dimethoxybenzylamino)-3H-quinazolin-4-one (process a)**

A mixture of 200 mg of 6-amino-3H-quinazolin-4-one and 206 mg of 2,5-dimethoxybenzaldehyde in 12 ml of dry methanol is heated to 60° for 16 hours. After cooling the yellow precipitate is filtered and resuspended in 10 ml of dry methanol. This mixture is treated with 85 mg of sodium cyanoborohydride and heated for some minutes until all the materials are dissolved. After stirring for 2 hours at room temperature, the mixture is poured into water and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and evaporated in vacuo. The pure title compound is obtained by crystallisation

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from ethanol as colourless crystals.

mp: 203-205°.

**Example 22: (2,5-Dimethoxyphenyl)ethyl]-4-hydroxy-3-quinoline-carboxylic acid ethylester (process b)**

1.48 g of diethyl {4-[2-(2,5-dimethoxyphenyl)ethyl]anilino)methylene-malonate are dissolved in 20 ml of warm diphenylether and heated to reflux for 30 minutes. The cold mixture is diluted with pentane, and the precipitate collected and dissolved in dichloromethane. The solution is dried over magnesium sulfate, and the solvent distilled off. The residue is crystallised from isopropanol to afford the title compound as yellowish crystals. mp: 195-198 °.

**Example 23: 6-(2,5-Dimethoxybenzyloxy)-3H-quinazolin-4-one (process b)**

90 mg of 5-(2,5-dimethoxybenzyloxy)-2-formylaminobenzamide are heated without solvent in a Kugelrohr apparatus at 170° for 1 hour. The resulting solid is purified by silica gel chromatography (ethyl acetate) to give colourless crystals. mp: 155-158°.

**Example 24: 3-(2,6-Dimethoxybenzyl)-6-(2,5-dimethoxybenzyloxy)-3H-quinazolin-4-one (process c)**

12 mg of sodium hydride (80% in mineral oil) are added to a solution of 115 mg of 3-(2,6-dimethoxybenzyl)-6-hydroxy-3H-quinazolin-4-one in 10 ml of dry dimethylformamide. After stirring for 30 minutes at room temperature, 85 mg of 2,5-dimethoxybenzylbromide are added, and stirring is continued overnight. The solvent is distilled off in vacuo, and the residue partitioned between aqueous pH7- buffer solution and ethyl acetate. The organic phase is separated, dried over magnesium sulfate and evaporated in vacuo. The pure title compound is obtained after silica gel chromatography (toluene/ethyl acetate = 2/1) as colourless crystals. mp: 148-150°.

Analogously as described in example 24 the following compounds of formula B and C are obtained:

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Ex.	form	W	R <sub>1</sub>	R <sub>2</sub>	Z	R <sub>10</sub>	Y	R <sub>9</sub>	m.p.
25	C	-CH <sub>2</sub> O-	OCH <sub>3</sub>	5-OCH <sub>3</sub>	O	2,5-DMB	-	-	92°
26	C	-CH <sub>2</sub> O-	OCH <sub>3</sub>	6-OCH <sub>3</sub>	O	2,6-DMB	-	-	167-170°
27	B	-CH <sub>2</sub> O-	OCH <sub>3</sub>	6-OCH <sub>3</sub>	-	-	N	OCH <sub>3</sub>	170-172°

2,5-DMB = 2,5-dimethoxybenzyl

2,6-DMB = 2,6-dimethoxybenzyl

**Example 28: (E)-6-[2-(2,5-Dimethoxyphenyl)ethenyl]-4-methoxyquinazoline**  
(process d)

At 0° under argon atmosphere, 500 mg of 2,5-dimethoxyphenylacetylene dissolved in 30 ml of dry tetrahydrofuran are treated with 450 mg of 9-borabicyclo[3.3.1]nonane. After stirring for 2 hours at room temperature, 650 mg of 6-iodo-4-methoxyquinazoline, 800 mg of potassium phosphate, 64 mg of tetrakis-(triphenylphosphine)palladium(0), and 15 ml of dioxane are added to the vinylborane intermediate. The mixture is stirred vigorously at 85° for 3 hours, then poured into water and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed on silica gel to give the title compound as yellowish oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 8.77 (s, 1H); 8.19 (d, J=2Hz, 1H); 8.10 (dd, J=2+8.8Hz, 1H); 7.90 (d, J=8.8Hz, 1H); 7.60 (d, J=16.5Hz, 1H); 7.24 (d, J=16.5Hz, 1H); 7.18 (d, J=2.4Hz, 1H); 6.80-6.90 (m, 2H); 4.21 (s, 3H); 3.88 (s, 3H); 3.84 (s, 3H).

Analogously as described in example 28 the following compound of formula B is obtained:

Ex.	W	R <sub>1</sub>	R <sub>2</sub>	Y	R <sub>9</sub>	m.p.
29	-CH=CH- (E)	OCH <sub>3</sub>	5-OCH <sub>3</sub>	N	C <sub>2</sub> H <sub>5</sub>	105°

**Example 30: 6-[2-(2,5-Dimethoxyphenyl)ethyl]-3-methyl-4-quinazolinon**

(process e)

34 mg of 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-quinazolinone are dissolved in 4 ml of dry dimethylformamide and treated with 4 mg of sodium hydride (80% in mineral oil). After stirring for 30 minutes, 0.1 ml of methyl iodide are added, and stirring is continued for 1 hour. The mixture is poured onto water and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. Silica gel chromatography (cyclohexane/ethyl acetate = 1/2) of the residue gives the title compound as colourless crystals. mp: 83-85°.

Analogously as described in example 30 the following compounds of formula B and C are obtained:

Ex	form	W	R <sub>1</sub>	R <sub>2</sub>	Y	R <sub>9</sub>	Z	R <sub>10</sub>	m.p.
31	C	-CH <sub>2</sub> CH <sub>2</sub> -	OCH <sub>3</sub>	5-OCH <sub>3</sub>	-	-	O	2,5-DMB	78-80°
32	C	-CH <sub>2</sub> O-	...	...	-	-	O	CH <sub>3</sub>	150°
33	B	-CH <sub>2</sub> CH <sub>2</sub> -	...	...	$\begin{array}{c} \text{---C=} \\   \\ \text{COOC}_2\text{H}_5 \end{array}$	OCH <sub>3</sub>	-	-	150- 151°
34	C	...	...	6-OCH <sub>3</sub>	-	-	O	2,6-DMB	140- 142°

**Example 35: 6-[2-(2,5-Dimethoxyphenyl)ethyl]-2,3-dihydro-1H-quinazolin-4-one**

(process e)

130 mg of 6-[2-(2,5-dimethoxyphenyl)ethyl]-3H-quinazolin-4-one are dissolved in 3 ml of acetic acid and treated with 58 mg of sodium borohydride. After stirring for 5 hours at room temperature, the mixture is poured onto 2 M aqueous pH7 buffer solution and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The residue is

chromatographed on silica gel to give the title compound as colourless crystals. mp.: 138-140°.

Analogously as described in example 35 the following compound of formula D is obtained:

Ex	W	R <sub>1</sub>	R <sub>2</sub>	Z	R <sub>10</sub>	m.p.
36	-CH <sub>2</sub> CH <sub>2</sub> -	OCH <sub>3</sub>	5-OCH <sub>3</sub>	O	CH <sub>3</sub>	110-112°

**Example 37: 4-Amino-6-[2-(2,5-dimethoxyphenyl)ethyl]-quinazoline (process e)**

A solution of 50 mg of 4-diacetyl-amino-6-[2-(2,5-dimethoxyphenyl)ethyl]-quinazoline and 10 ml of 1 N aqueous sodium hydroxide solution in dioxane is stirred for 3 hours at room temperature. The mixture is poured onto water and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated in vacuo. The residue is taken up in methanol, stirred for 30 minutes, filtered and concentrated again. Chromatographic purification (silica gel, ethyl acetate) gives the title compound as colourless crystals. mp.: 160-165°.

**Example 38: 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-isopropoxyquinazoline (process e)**

150 mg of 6-[2-(2,5-dimethoxyphenyl)ethyl]-3H-quinazolin-4-one are heated together with 5 ml of phosphorus oxychloride and 100 mg of phosphorus pentachloride at reflux for 30 minutes. The mixture is concentrated in vacuo and then partitioned between ice-cold 2 M aqueous pH 7 buffer and ethyl acetate. The organic layer is separated, dried and evaporated in vacuo to yield crude 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-chloroquinazoline, which can be directly used in the following step or purified by chromatography (silica gel, cyclohexane/ethyl acetate = 1/1). The crude intermediate is added to a solution of sodium isopropoxide (prepared from 8.3 mg of sodium in 20 ml of isopropanol) in isopropanol. The mixture is refluxed for 1 hour, concentrated in vacuo and poured onto water. Extraction with ethyl acetate yields the crude title compound, which is purified by

chromatography on silica gel (cyclohexane/ethyl acetate = 2/1) to give a colourless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 8.73 (s, 1H); 7.92 (d, J=2Hz, 1H); 7.82 (d, J=8.5Hz, 1H); 7.66 (dd, J=2+8.5Hz, 1H); 6.68-6.80 (m, 3H); 5.62 (sep, J=6.2Hz, 1H); 3.77 (s, 3H); 3.71 (s, 3H); 2.91-3.1 (m, 4H); 1.47 (d, J=6.2Hz, 6H).

Analogously as described in example 38 the following compounds of formula I are obtained:

Ex	form	W	R <sub>1</sub>	R <sub>2</sub>	Y	R <sub>9</sub>	Z	R <sub>1</sub> o	m.p.:
39	B	-CH <sub>2</sub> CH <sub>2</sub> -	OCH <sub>3</sub>	5-OCH <sub>3</sub>	N	SCH <sub>3</sub>	-	-	95°
40	C	-	-	-	-	-	S	H	185-190°

**Example 41: 6-[2-(5-Hydroxy-2-methoxyphenyl)ethyl]-3H-quinazolin-4-one**  
(process e)

90 mg of 6-[2-(5-hydroxy-2-methoxyphenyl)ethyl]-4-methoxyquinazoline are dissolved in 8 ml of methanol and treated with 1 ml of 4 N aqueous hydrochloric acid. The mixture is stirred for 16 hours at room temperature, then poured onto 2 M aqueous pH 7 buffer and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and evaporated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol = 9/1) to yield the title compound as colourless crystals. mp: 221-224°.

**Exempl 42: 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-methoxycarbonyl-amino benz ic acid methylester (process e)**

A mixture of 115 mg of 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-amino benzoic acid methylester and 50 mg of 4-dimethylaminopyridine in 6 ml of dry dichloromethane is treated with 35 mg of methyl chloroformate and stirred for 3 hours at room temperature. Then the mixture is poured onto aqueous pH7 buffer solution and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated in vacuo. The crude product is purified by silica gel chromatography (cyclohexane/ethyl acetate = 8/1) to yield the title compound as colourless crystals. mp: 80-82 °.

**Example 43: 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-methylamino benzoic acid methylester (process e)**

110 mg of 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-amino benzoic acid methylester are dissolved in 6 ml of dry dimethylformamide and treated with 13 mg of sodium hydride (80% in mineral oil). After stirring for 30 minutes at room temperature, 0.2 ml of methyl iodide are added and stirring continued overnight. The solvent is distilled off in vacuo, and the residue is partitioned between aqueous pH7 buffer solution and ethyl acetate. The separated organic layer is dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed on silica gel (hexane/ethyl acetate = 7/1) to give the title compound as colourless crystals. mp: 73 °.

Analogously as described in example 43 the following compound of formula A is obtained:

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	X	m.p.
44	OCH <sub>3</sub>	5-OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	O	oil


**Example 45: 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-acetyl amino benzoic acid  
thylester (process d)**

A mixture of 93 mg of 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-acetyl amino-benzoic acid butylester, 100 mg of lithium bromide, 55 mg of 1,8-diazabicyclo[5.4.0]undec-7-en and 4 ml of dry ethanol is heated to reflux for 3 hours. After neutralisation with 0.1 N aqueous hydrochloric acid, the mixture is extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated in vacuo. The pure title compound is obtained by silica gel chromatography (hexane/ethyl acetate = 6/1) as colourless crystals. mp: 93°.

Analogously as described in example 45 the following compound of formula A is obtained:

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	X	m.p.
46	OCH <sub>3</sub>	6-OCH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	Ac	H	O	87-90°

Analogously as described in example 45 the following compound of formula B is obtained:

Ex	W	R <sub>1</sub>	R <sub>2</sub>	Y	R <sub>9</sub>	m.p.
47	CH <sub>2</sub> CH <sub>2</sub>	OCH <sub>3</sub>	5-OCH <sub>3</sub>		OH	189-193°

**Example 48: 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-amino benzoic acid  
methylester (process e)**

87 mg of 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-acetyl amino benzoic acid methylester are dissolved in 6 ml of methanol, treated with 1 ml of 4 N hydrochloric acid and stirred for 48 hours at room temperature. The mixture is neutralised by addition of

2 N aqueous sodium hydroxide solution and extracted with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. Purification by chromatography on silica gel (hexane/ethyl acetate = 6/1) yields the title compound as colourless crystals. mp: 50-55°.

Analogously as described in example 48 the following compounds of formula A are obtained:

Ex	R <sub>1</sub>	R <sub>2</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	X	m.p.
49	OCH <sub>3</sub>	6-OCH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	H	O	53-55°
50	-"	5-OCH <sub>3</sub>	-"	H	H	O	oil
51	-"	6-OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	O	90-93°

**Example 52: 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-hydroxy-quinoline (process e)**

a) 300 mg of 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-hydroxy-3-quinolinecarboxylic acid ethylester are dissolved in 10 ml of methanol, treated with 6 ml of 10 % aqueous potassium hydroxide solution and heated to reflux for 2 hours. The mixture is poured onto 1 N hydrochloric acid and extracted with dichloromethane containing 3% of ethanol. The organic layers are dried over magnesium sulfate and evaporation of the solvent yields the corresponding free carboxylic acid as colourless crystals. mp: 148-151°.

b) 150 mg of 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-hydroxy-3-quinolinecarboxylic acid are dissolved in hot diphenylether, and the solution is heated to reflux for 1 hour. The cold reaction mixture is diluted with ethyl acetate and extracted with 6 N hydrochloric acid. The acidic aqueous layers are combined, washed with ethyl acetate, and then neutralised (pH 7) using aqueous ammonium hydroxide solution.

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Extraction with ethyl acetate, drying over magnesium sulfate and evaporation yields a crude product, which is purified by chromatography on silica gel (dichloromethane/methanol = 95/5) to give the title compound as yellowish crystals. mp: 141-145°.

Analogously as described in example 52 the following compound of formula B is obtained:

Ex.	W	R <sub>1</sub>	R <sup>2</sup>	Y	R <sub>9</sub>	
53	-CH <sub>2</sub> CH <sub>2</sub> -	OCH <sub>3</sub>	5-OCH <sub>3</sub>	-CH=	OCH <sub>3</sub>	oil

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 8.36 (d, J = 2 Hz, 1H); 7.52 (dd, J = 2 + 8.6 Hz, 1H); 7.48 (d, J = 7.7 Hz, 1H); 7.32 (d, J = 8.6 Hz, 1H); 6.68 - 6.78 (m, 3H); 6.26 (d, J = 7.7 Hz); 3.80 (s, 3H); 3.79 (s, 3H); 3.74 (s, 3H); 2.90 - 3.04 (m, 4H).

The starting materials may be prepared in the following manner:

**A) 5-[2-(2,5-Dimethoxyphenyl)ethenyl]-2-acetylamino benzoic acid methylester**  
4.1 mmol of n-butyllithium (0.4 ml of 1.6 M solution in hexane) are added at -40° to a solution of 412 mg of diisopropylamine in 30 ml of dry tetrahydrofuran. After stirring for 30 minutes 672 mg of 2,5-dimethoxybenzyl-triphenylphosphonium bromide are added at this temperature. The suspension is stirred for another 30 minutes, cooled to -70° and treated with 300 mg of 2-acetylamino-5-formyl-benzoic acid methylester in 8 ml of absolute tetrahydrofuran. The mixture is stirred for one hour at -70° and for two hours at room temperature and then poured onto aqueous ammonium chloride solution. Extraction with ethyl acetate and evaporation yields a crude product, which is subjected to silica gel chromatography (hexane/ethyl acetate = 9/1) to obtain the title compound as a mixture of the E- and Z-isomers.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 11.05 (s, 1H E-isomer); 11.00 (s, 1H Z-isomer); 8.72 (d, J=8.8Hz, 1H E-isomer); 8.52 (d, J=8.8Hz, 1H Z-isomer); 8.16 (d, J=2.2Hz, 1H E-isomer); 7.95

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(d, J=2.2Hz, 1H Z-isomer); 7.74 (dd, J=2.2+8.8Hz, 1H E-isomer); 7.42 (dd, J=2.2+8.8Hz, 1H Z-isomer); 7.41 (d, J=16.4Hz, 1H E-isomer); 7.14 (d, J=2.6Hz, 1H E-isomer); 7.05 (d, J=16.4Hz, 1H E-isomer); 6.72-6.89 (m); 6.67 (d, J=12.2Hz, 1H Z-isomer); 6.55 (d, J=12.2Hz, 1H Z-isomer); 3.97 (s, 3H E-isomer); 3.87 (s); 3.83 (s, 3H E-isomer); 3.78 (s, 3H Z-isomer); 3.59 (s, 3H Z-isomer); 2.25 (s, 3H E-isomer); 2.22 (s, 3H Z-isomer).

**B) (E)-5-[2-(2,6-Dimethoxyphenyl)ethenyl]-2-acetylamino benzoic acid methylester**

The title substance is obtained analogously as described under A)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 11.07 (s, 1H); 8.68 (d, J=8.8Hz, 1H); 8.13 (d, J=2.2Hz, 1H); 7.76 (dd, J=2.2+8.8Hz, 1H); 7.54 (d, J=16.6Hz, 1H); 7.41 (d, J=16.6Hz, 1H); 7.18 (t, J=8.3Hz, 1H); 6.60 (d, J=8.3Hz, 2H); 3.96 (s, 3H); 3.91 (s, 6H); 2.25 (s, 3H).

**C) (E/Z)-5-[2-(2,5-Dimethoxyphenyl)ethenyl]-2-acetylamino-benzoic acid butylester**

The title substance is obtained analogously as described under A)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 11.10 (s, 1H E-isomer); 11.06 (s, 1H Z-isomer); 8.70 (d, J=8.8Hz, 1H E-isomer); 8.54 (d, J=8.8Hz, 1H Z-isomer); 8.12 (d, J=2.2Hz, 1H E-isomer); 7.96 (d, J=2.2Hz, 1H Z-isomer); 7.74 (dd, J=2.2+8.8Hz, 1H E-isomer); 7.42 (dd, J=2.2+8.8Hz, 1H Z-isomer); 7.41 (d, J=16.4Hz, 1H E-isomer); 7.14 (d, J=2.6Hz, 1H E-isomer); 7.05 (d, J=16.4Hz, 1H E-isomer); 6.72-6.89 (m); 6.67 (d, J=12.2Hz, 1H Z-isomer); 6.55 (d, J=12.2Hz, 1H Z-isomer); 4.36 (t, J=6.5Hz, 2H E-isomer); 4.23 (t, J=6.5Hz, 2H Z-isomer); 3.86 (s, 3H E-isomer); 3.82 (s, 3H E-isomer); 3.77 (s, 3H Z-isomer); 3.58 (s, 3H Z-isomer); 2.24 (s, 3H E-isomer); 2.21 (s, 3H Z-isomer); 1.20-1.85 (m); 1.02 (t, J=7.3Hz, 3H E-isomer); 0.96 (t, J=7.3Hz, 3H Z-isomer).

**D) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-ethyl-quinazoline**

**a) 6-Iodo-4-ethyl-quinazoline**

154 mg of sodium are dissolved in 20 ml of dry methanol and treated with 1.2 g of 4-chloro-6-iodo-quinazoline. The mixture is heated to reflux for 1 hour, and then the

solvent is distilled off. The residue is partitioned between aqueous pH7 buffer solution and ethyl acetate. The aqueous layer is extracted with ethyl acetate, and the combined organic extracts are dried over magnesium sulfate and evaporated in vacuo. The residue is dissolved in cyclohexane/ethyl acetate (1/1) and filtered over silica gel. The title compound is obtained as slightly yellowish crystals after evaporation of the solvent.

mp: 110-113°.

**b) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-ethyl-quinazoline**

Argon is passed through a solution of 200 mg of 6-iodo-4-methoxy-quinazoline in 12 ml of dry dimethylformamide for 15 minutes. Then 40 mg of tetrakis(triphenylphosphine)-palladium, 113 mg of (2,5-dimethoxyphenyl)acetylene, 11 mg of copper(I)iodide and 220 mg of triethylamine are added, and the mixture is heated to 60° for 2 hours. The solvent is distilled off in vacuo and the residue partitioned between water and ethyl acetate. The organic layer is separated, dried and concentrated in vacuo. The pure title compound is obtained after chromatography (silica gel, cyclohexane/ethyl acetate = 2/1) as colourless crystals. mp: 103-105°.

Analogously as described in D) the following compounds of formula IIb (E-Q) are obtained:

**E) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]quinazolin-4-one, mp: 180-183°**

**F) 6-[2-(2,6-Dimethoxyphenyl)ethynyl]-4-methoxy-quinazoline, mp: 140-142°**

**G) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-ethoxy-quinazoline, mp: 75-77°**

**H) 6-[2-(2,6-Dimethoxyphenyl)ethynyl]quinazolin-4-one, mp: 219-221°**

**I) 6-[2-(2-Benzoyloxy-5-methoxyphenyl)ethynyl]-4-methoxy-quinazoline, mp: 112-114°**

**J) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-methyl-quinazoline, mp: 113-116°**

**K) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-methoxy-quinazoline, mp: 103-105°**

**L) 6-[2-(2,5-Diethylphenyl)ethynyl]-4-ethyl-quinazoline, mp: 56°**

**M) 6-[2-(2,6-Dimethoxyphenyl)ethynyl]-4-ethyl-quinazoline, mp: 155-157°**

**N) 5-[2-(2,5-Dimethoxyphenyl)ethynyl]-2-amino-benzamide**

<sup>1</sup>H-NMR(d<sub>6</sub>-DMSO): 7.90 (br.s, 1H); 7.75 (d, J=2Hz, 1H); 7.27 (dd, J=2+8.5Hz, 1H); 7.15 (br.s, 1H); 6.93-7.05 (m, 4H); 6.90 (dd, J=3+8.8Hz, 1H); 6.71 (d, J=8.5Hz, 1H); 3.79 (s, 3H); 3.72 (s, 3H).

**O) 6-[2-(2,5-Diethoxyphenyl)ethynyl]-4-ethyl-quinazoline**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.21 (s, 1H); 8.30 (m, 1H); 7.93-8.04 (m, 2H); 7.08 (m, 1H); 6.82-7.1 (m, 2H); 4.13 (qua, J=7Hz, 2H); 4.02 (qua, J=7Hz, 2H); 3.32 (qua, J=7.5Hz, 2H); 1.50 (t, J=7Hz, 3H); 1.48 (t, J=7.5Hz, 3H); 1.41 (t, J=7Hz, 3H).

**P) 6-[2-(5-Benzyloxy-2-methoxyphenyl)ethynyl]-4-methoxyquinazoline**

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 8.81 (s, 1H); 8.37 (d, J = 1.8 Hz, 1H); 7.96 (dd, J = 1.8+8.6 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H); 7.30-7.50 (m, 5H); 7.18 (d, J = 3 Hz, 1H); 6.98 (dd, J = 3+9 Hz, 1H); 6.85 (d, J = 9 Hz, 1H); 5.05 (s, 2H); 6.20 (s, 3H); 3.90 (s, 3H).

**Q) 6-[2-(2,5-Dimethoxyphenyl)]quinazoline**

mp: 100-102°

**R) 4-Diacetylamino-6-[2-(2,5-dimethoxyphenyl)ethynyl]quinazoline**

**a) 4-Amino-6-iodo-quinazoline**

500 mg of 4-chloro-6-iodo-quinazoline are treated with 30 ml of aqueous ammonium hydroxide solution and heated to reflux for 2 hours. After cooling the precipitated title compound is filtered and dried.

<sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 8.66 (d, J = 1.8 Hz, 1H), 8.4 (s, 1H), 8.02 (dd, J = 1.8 + 8.7 Hz, 1H), 7.85 (br s, 2H), 7.45 (d, J=8.7 Hz, 1H).

**b) 4-Diacetylamino-6-iodo-quinazoline**

A mixture of 340 mg of 4-amino-6-iodo-quinazoline, 1 ml of pyridine, and 20 ml of acetic anhydride is heated to 80° for 1 hour. The cold mixture is poured onto ice/water, stirred vigorously and extracted with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated in vacuo. The title compound is obtained by chromatographic purification on silica gel (ethyl acetate/cyclohexane = 2/1).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.36 (s, 1H), 8.22 (dd, J = 1.9 + 8.9 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1 H), 2.34 (s, 6H).

**c) 4-Diacetylamino-6-[2-(2,5-dimethoxyphenyl)ethynyl]-quinazoline**

The title substance is obtained analogously as described under C/b.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 9.33 (s, 1H), 8.09 (dd, J = 0.7 + 8.8 Hz, 1H), 8.04 (dd, J = 1.65 + 8.8 Hz, 1H), 7.95 (dd, J = 0.7 + 1.65 Hz, 1H), 7.06 (d, J = 2.9 Hz, 1H), 6.90 (dd, J = 2.9 + 9 Hz, 1H), 6.82 (d, J = 9 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 2.30 (s, 6H).

**S) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-methylamino-quinazoline**

**a) 6-Iodo-4-methylamino-quinazoline:**

Prepared analogously to the method described for the synthesis of 4-amino-6-iodo-quin-azoline. mp: 245°.

**b) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-methylamino-quinazoline**

The title substance is obtained analogously as described under D/b.

**T) 6-[2-(2,5-Dimethoxyphenyl)ethynyl]-quinazoline**

**U) Diethyl {4-[2-(2,5-dimethoxyphenyl)ethyl]anilino}methylene-malonate**

The mixture of 820 mg of 4-[(2,5-dimethoxyphenyl)ethyl]aniline and 690 mg of diethyl ethoxymethylene-malonate is heated to 95° for 2 hours. On cooling the product crystallises and is used without further purification.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): 10.98 (d, J = 13.8 Hz, 1H), 8.51 (d, J = 13.8 Hz, 1H), 7.14 - 7.22 (m, 2H), 7.01 - 7.09 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 6.70 (dd, J = 3 + 8.7 Hz, 1H), 6.66 (d, J = 3 Hz, 1H), 4.31 (qua, J = 7.1 Hz, 2H), 4.24 (qua, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 2.86 (s, 4H), 1.38 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H).

**V) 5-(2,5-Dimethoxybenzyloxy)-2-formylaminobenzamide**

A solution of 140 mg of 2-formylamino-5-hydroxybenzamide in 15 ml of dry dimethylformamide is treated subsequently with 160 mg of potassium carbonate and 180 mg of 2,5-dimethoxybenzylbromide. The mixture is stirred at room temperature

for 4 hours, and then the solvent is distilled off in vacuo. The residue is partitioned between water and ethyl acetate, and the separated organic layer is dried over magnesium sulfate and evaporated in vacuo. Purification of the crude product thus obtained by silica gel chromatography (ethyl acetate) gives the title compound as colourless crystals. mp: 135-138°.

**W) 3-(2,6-Dimethoxybenzyl)-6-hydroxy-3H-quinazolin-4-one**

76 mg of sodium hydride (80% in mineral oil) are added to a suspension of 400 mg of 6-hydroxy-3H-quinazolin-4-one in 20 ml of dry dimethylformamide. After stirring for 30 minutes at room temperature, 560 mg of 2,6-dimethoxybenzylbromide are added, and stirring is continued overnight. The solvent is distilled off in vacuo, and the residue partitioned between aqueous pH7-buffer solution and ethyl acetate. The organic phase is separated, dried over magnesium sulfate and evaporated in vacuo. Silica gel chromatography yields a minor amount of the N,O-bis-alkylated product followed by the pure title compound as colourless crystals. mp: 243-245°.

**X) 3-(2,5-Dimethoxybenzyl)-6-hydroxy-3H-quinazolin-4-one**

Prepared analogously as described under V).  
mp: 203°.

**Y) 6-Hydroxy-4-methoxyquinazoline**

A mixture of 200 mg of 6-hydroxy-3H-quinazolin-4-one and 5 ml of phosphorylchloride is heated to reflux for 2 hours. The excess phosphorylchloride is distilled off in vacuo and the residue is taken up in a solution of sodium methoxide (prepared from 80 mg sodium) in dry methanol. After refluxing for 2 hours the solvent is distilled off and the residue is partitioned between aqueous pH7-buffer solution and ethyl acetate. The organic phase is separated, dried over magnesium sulfate and evaporated in vacuo. The crude product is directly used in the next reaction or purified by chromatography on silica gel.

<sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 10.25 (br.s,1H); 8.61 (s,1H); 7.79 (d,J=9Hz,1H); 7.45 (dd,J=2.8+9Hz,1H); 7.32 (d,J=2.8Hz,1H); 4.09 (s,3H).

The compounds of this invention possess advantageous chemotherapeutical properties and exhibit on local, systemic or oral application antiproliferative/antiinflammatory and/or anticancer activity. These activities can be shown in the following tests, wherein the following abbreviations are used:

BSA = bovine serum albumin  
HaCaT = the cell line known as "human adult calcium temperature"  
HeLa-O = tumor cell line from human cervix  
A375 = human melanoma cell line  
A549 = human lung carcinoma cell line  
MDA-MB-231 = human breast carcinoma cell line  
SW-480 = human colon carcinoma cell line  
DMEM = Dulbecco's modified eagle medium  
EGF = epidermal growth factor  
FCS = fetal calf serum  
TGF $\alpha$  = transforming growth factor  $\alpha$   
BSA = bovine serum albumin  
MDA-MB-435 = human breast carcinoma cell line  
HT-29 = human colon carcinoma cell line

#### **1. Inhibition of proliferation in the human keratinocyte cell line HaCaT:**

HaCaT cells, a spontaneously transformed, TGF $\alpha$ - and EGF-receptor positive non-tumorigenic human keratinocyte cell line with highly preserved phenotypic differentiation characteristics of normal keratinocytes (Boukamp et al., J. Cell. Biol. 106: 761-771[1988]), are cultivated in DMEM medium supplemented with 2.2 g/l NaHCO<sub>3</sub>, 0.11 g/l sodium pyruvate, 15 mM Hepes, 5% fetal calf serum (FCS), penicillin (100 U/ml), streptomycin (100  $\mu$ g/ml), and glutamine (to increase the final concentration by 4 mM). For the proliferation assay, cells are detached by trypsinization, suspended in fresh medium, and seeded into 96-well microtiter plates at 2000 - 4000 cells/0.2 ml/well. After 24 hours the medium is replaced with fresh medium containing graded concentrations of test compound. After 3-4 days of incubation, the extent of cellular proliferation is measured by a colorimetric assay

using sulforhodamine B (Skehan et al., J. Natl. Canc. r Inst. 82: 1107-1112 [1990]). The results represent the average  $\pm$  standard deviation of three measurements.

In this test the compounds of the invention inhibit cell proliferation with  $IC_{50}$ -values ranging from about 0.003  $\mu$ M to about 3  $\mu$ M.

## **2. Inhibition of tumor cell proliferation:**

Tumor cell lines, for example A375, A549, HeLa-O, MDA-MB-231, SW-480, MDA-MB 435 and HT-29, available from American Type Culture Collection, are grown in medium supplemented with 5 to 10% heat inactivated (56° C/30 min) FCS and antibiotics. At the time of 60-90% confluence the cells are harvested, trypsinized, suspended in fresh growth medium and seeded into 96 well cell culture plates at concentrations ranging between 1000 and 5000 cells/well. Cells are grown for 3 - 4 days in a final volume of 0.2 ml/well, at 37° C in an humidified incubator equilibrated with 5% CO<sub>2</sub>, in the presence of graded concentrations of test compound. Extent of cellular proliferation is measured by a colorimetric assay using MTS (Buttke et al., J. Immunol. Meth. 157: 233-240 [1993]) for cells growing in suspension or by sulforhodamine B for adherent cells. In this experimental system the compounds of this invention inhibit cell proliferation with  $IC_{50}$  ranging between 0.01 and 5  $\mu$ M.

The compounds of the invention are therefore indicated for use as antiproliferative /antiinflammatory and anticancer agents in the treatment of proliferative/inflammatory disorders and cancer such as in suppression of neoplastic diseases, e.g. inflammatory/proliferative skin diseases and skin cancer, and autoimmune diseases, such as: psoriasis, atopic dermatitis, contact dermatitis and related eczematous dermatitises, seborrheic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and Alopecia areata.

For this use the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment

desired. However, in general, satisfactory results are obtained when the compounds are administered at a daily dosage of from about 1 mg/kg to about 30 mg/kg animal body weight, suitably given in divided doses two to four times daily. For most large mammals the total daily dosage is from about 70 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Unit dosage forms comprise, for example, from about 17.5 mg to about 1000 mg of the compounds in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

The compounds of the invention may be administered in similar manner to known standards for use in such indications. The compounds may be admixed with conventional chemotherapeutically acceptable carriers and diluents and, optionally, further excipients, and administered e.g. orally in such forms as tablets and capsules.

Alternatively, the compounds may be administered topically in such conventional forms as ointments or creams, parenterally or intravenously. The concentrations of the active substance will, of course vary depending e.g. on the compound employed, the treatment desired and the nature of the form. In general, however, satisfactory results are obtained, e.g. in topical application forms at concentrations of from about 0.05 to about 5%, particularly from about 0.1 to about 1% by weight.

Pharmaceutical compositions comprising a compound of the invention together with at least one pharmaceutically acceptable carrier or diluent also form part of the invention, as well as a process for the preparation thereof by mixing together with at least one pharmaceutically acceptable carrier or diluent. The invention also comprises the compounds of the invention for use as pharmaceuticals, especially in the prevention or treatment of inflammatory and proliferative skin illnesses and cancer.

The invention further comprises a method of prevention or treatment of inflammatory and proliferative skin diseases and cancer, which comprises administering a



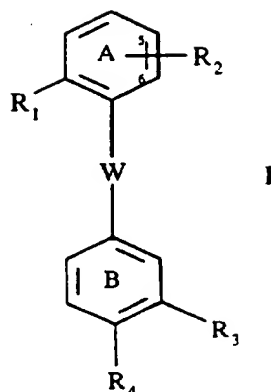
therapeutically effective amount of a compound of the invention to a subject in need of such treatment.

The compounds of the invention of formula Is and especially the compounds of formula Iss are particularly preferred.

The compounds of example 6, 16 and 17, namely 6-[2-(2,5- dimethoxyphenyl)ethyl]-4-ethyl-quinazoline and, respectively, the corresponding 4-methoxy and 4-methyl compounds, are the most preferred compounds as antiproliferative/antiinflammatory and anticancer agents, especially the compound of Example 6. It has, for example, been determined that in the above test 1 these 3 compounds have an  $IC_{50}$  of about 10 nM, in the above test 2 an  $IC_{50}$  between 10 and 200 nM.

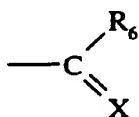
**Claims:**

## 1. Compounds of formula

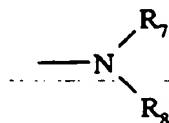


wherein  $R_1$  and  $R_2$  are the same or different and represent hydroxy, alkoxy, acyloxy, alkyl or acyl, whereby  $R_2$  is in the 5- or 6-position, with the proviso that  $R_1$  and  $R_2$  are not simultaneously hydroxy or acyloxy, and

a)  $W$  represents  $-\text{CH}_2\text{CH}_2-$ ,  $R_3$  represents a group of formula



wherein  $R_6$  represents hydrogen, alkyl, alkoxy or amino and  $X$  represents oxygen, hydroxyimino or alkoxyimino,  $R_4$  represents a group of formula



wherein  $R_7$  and  $R_8$  are the same or different and represent hydrogen, alkyl, acyl or alkoxycarbonyl, or

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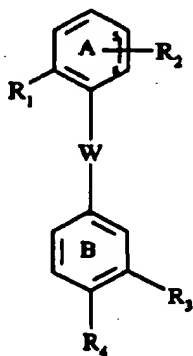
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(51) International Patent Classification <sup>6</sup> : <b>C07D 239/88, 239/74, 239/94, C07C 229/56, 237/30, C07D 215/22</b>		A1	(11) International Publication Number: <b>WO 96/28430</b>
		(43) International Publication Date: 19 September 1996 (19.09.96)	
(21) International Application Number: PCT/EP96/01116		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 14 March 1996 (14.03.96)		<p><b>Published</b> With international search report.</p>	
(30) Priority Data:			
9505080.3 14 March 1995 (14.03.95) GB			
9505858.2 23 March 1995 (23.03.95) GB			
9526593.0 28 December 1995 (28.12.95) GB			
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(54) Title: TRISUBSTITUTED PHENYL DERIVATIVES



(57) Abstract

The invention concerns compounds of formula (I), wherein the substituents have various meanings, and their use in the prevention or treatment of inflammatory and proliferative skin diseases and cancer.

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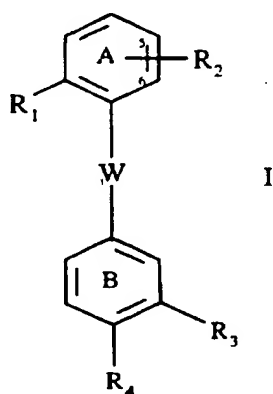
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# TRISUBSTITUTED PHENYL DERIVATIVES

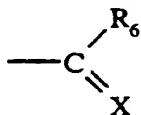
The present invention concerns new organic compounds, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals especially for the treatment of proliferative and/or inflammatory disorders and cancer.

More particularly the invention concerns compounds of the formula



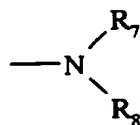
wherein  $R_1$  and  $R_2$  are the same or different and represent hydroxy, alkoxy, acyloxy, alkyl or acyl, whereby  $R_2$  is in the 5- or 6-position, with the proviso that  $R_1$  and  $R_2$  are not simultaneously hydroxy or acyloxy, and

a) W represents  $-\text{CH}_2\text{CH}_2-$ ,  $R_3$  represents a group of formula



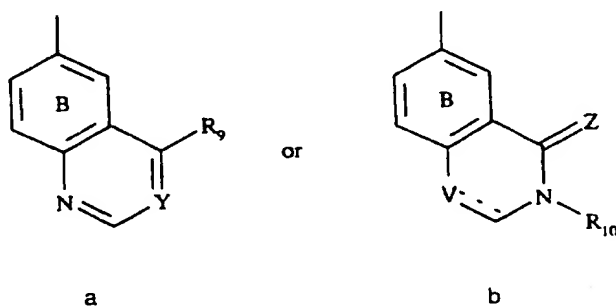
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wherein  $R_6$  represents hydrogen, alkyl, alkoxy or amino and X represents oxygen, hydroxyimino or alkoxyimino,  $R_4$  represents a group of formula



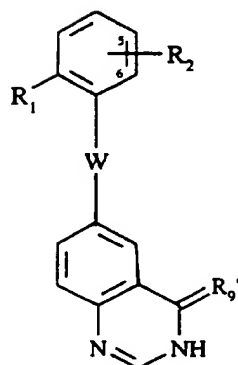
wherein  $R_7$  and  $R_8$  are the same or different and represent hydrogen, alkyl, acyl or alkoxy carbonyl, or

b) W represents  $\text{---CH}_2\text{CH}_2\text{---}$ ,  $\text{---CH=CH---}$ ,  $\text{---CH}_2\text{O---}$  or  $\text{---CH}_2\text{NR}_5\text{---}$ , whereby the heteroatom adheres to ring B and  $R_5$  represents hydrogen, alkyl or acyl,  $R_3$  and  $R_4$  form together with the adjacent ring B a condensed ring system of formula



wherein the symbol  $\text{---}$  represents a single or a double bond,  $R_9$  represents hydrogen, alkylthio, alkyl, alkoxy carbonyl, acyl, amino, acylamino, diacylamino, alkylamino, dialkylamino, cyano, hydroxy, alkoxy or mercapto, Y represents N or  $\text{CR}_{11}$ ,  $R_{10}$  represents hydrogen, alkyl, acyl or optionally substituted phenylalkyl,  $R_{11}$  represents hydrogen, alkoxy carbonyl, cyano or acyl, Z represents O or S and V represents NH, if the symbol  $\text{---}$  represents a single bond, and N, if the symbol  $\text{---}$  represents a double bond, with the proviso that, if  $R_9$  represents hydroxy or mercapto and Y represents N, the compounds exist predominantly in the tautomeric form of formula

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It

wherein  $R_9'$  represents O or S, in free form or, where such forms exist, in salt form, herein briefly named "compounds of the invention".

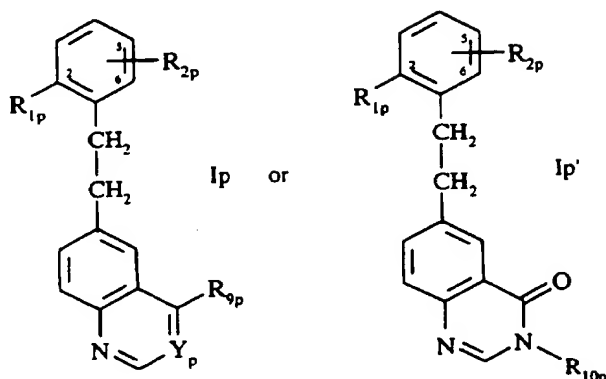
The compounds of the invention possess interesting pharmacological, in particular antiproliferative, antiinflammatory and antitumor activity.

Alkyl as such or as part of a substituent such as alkoxy preferably is of 1 to 4 carbon atoms, it particularly is methyl or ethyl. Acyl preferably is the residue of a carboxylic acid, in particular an alkyl, arylalkyl or aryl carboxylic acid, whereby aryl preferably is phenyl, and the alkylene part of acyl, including the carbonyl group, preferably is of 1 to 5 carbon atoms. A preferred acyl moiety is acetyl.

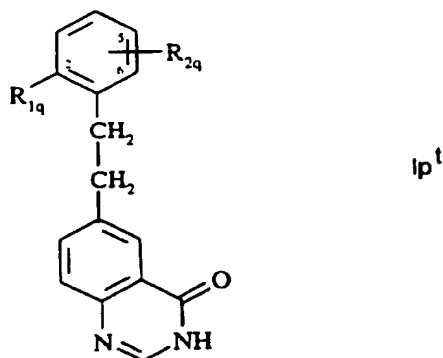
In a preferred group of compounds of the invention  $R_1$  and  $R_2$  independently are alkoxy of 1 to 4 carbon atoms,  $W$  represents  $-\text{CH}_2\text{CH}_2-$  and  $R_3$  and  $R_4$  represent a condensed ring system as defined above.

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A preferred group are compounds of formula



wherein  $R_{1p}$  and  $R_{2p}$  are the same or different and represent hydroxy, alkoxy, acyloxy, alkyl or acyl, whereby  $R_{2p}$  is in the 5- or 6-position, with the proviso that  $R_{1p}$  and  $R_{2p}$  are not simultaneously hydroxy or acyloxy,  $R_{9p}$  represents hydrogen, alkyl, alkoxycarbonyl, acyl, amino, acylamino, diacylamino, alkylamino, dialkylamino, cyano, alkoxy or hydroxy,  $Y_p$  represents N or CH and  $R_{10p}$  represents hydrogen, alkyl or acyl, with the proviso that, if  $R_{9p}$  represents hydroxy and  $Y_p$  represents N, the compounds exist predominantly in the tautomeric form of formula

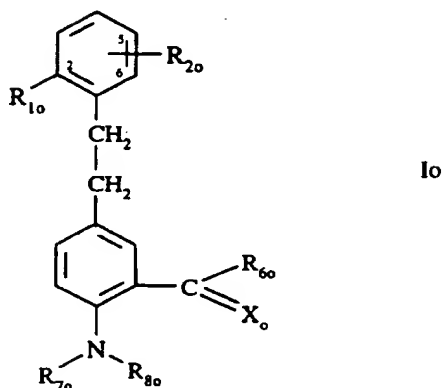


in free form, or where such forms exist, in salt form.

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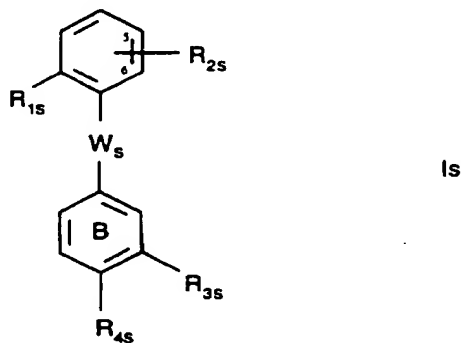
A further preferred group are compounds of formula



wherein  $R_{10}$  and  $R_{20}$  are the same or different and represent alkyl, acyl or alkoxy, and  $R_{60}$ ,  $R_{70}$ ,  $R_{80}$  and  $X_0$  have the same significance as  $R_6$ ,  $R_7$ ,  $R_8$  and  $X$ , in free form or, where such forms exist, in salt form.

Unless otherwise stated alkyl moieties are preferably straight or branched chains having 1 to 12, especially 1 to 8 carbon atoms, particularly 1 to 6 and especially 1 to 4. Any lower alkyl present as or in a substituent is straight or branched-chain and has preferably 1 to 4, especially 1 or 2 carbon atoms.

A further preferred group of compounds of the invention is the compounds of formula



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wherein

$R_{1s}$  is hydroxy, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

$R_{2s}$  is hydroxy or alkoxy of 1 to 4 carbon atoms and is in the 5- or 6-position,

whereby  $R_{1s}$  and  $R_{2s}$  are not simultaneously hydroxy; and

a)  $W_s$  is  $-\text{CH}_2\text{CH}_2-$ ;

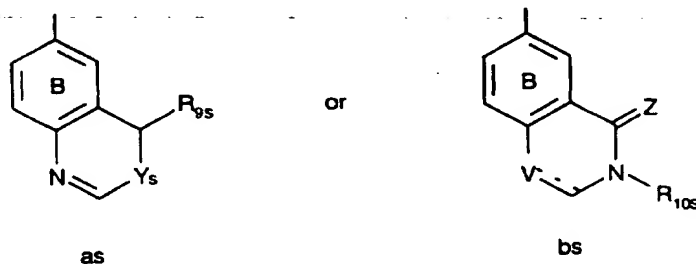
$R_{3s}$  is a group of formula  $-\text{COR}_{6s}$  wherein

$R_{6s}$  is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or amino; and

$R_{4s}$  is amino, alkylamino of 1 to 4 carbon atoms, dialkylamino independently of 1 to 4 carbon atoms in each alkyl part thereof, alkylcarbonylamino of 1 to 4 carbon atoms in the alkyl part thereof, or alkoxy carbonylamino of 1 to 4 carbon atoms in the alkoxy part thereof; or

b)  $W_s$  is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{NH}-$ ,  $-\text{CH}_2\text{O}-$  or  $-\text{CH}=\text{CH}-$ , whereby the nitrogen or oxygen atom is bound to ring B; and

$R_{3s}$  and  $R_{4s}$  together with ring B form a condensed ring system of formula



wherein

the symbol  $---$  is a single or a double bond;

$R_{9s}$  is hydrogen, alkylthio of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms, amino, diacetylamino, alkylamino of 1 to 4 carbon atoms, hydroxy, alkoxy of 1 to 4 carbon atoms or mercapto;

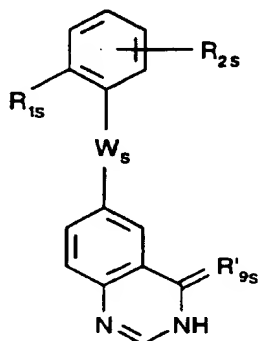
$Y_s$  is N or  $\text{CR}_{11s}$  wherein  $R_{11s}$  is hydrogen or alkoxy carbonyl of 1 to 4 carbon atoms in the alkoxy part thereof,

$R_{10s}$  is hydrogen, alkyl of 1 to 4 carbon atoms or dialkoxybenzyl independently of 1 to 4 carbon atoms in the alkoxy parts thereof; and

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Z and V are as defined above;

with the proviso that, if  $R_{9s}$  is hydroxy or mercapto and  $Y_s$  is N, then the compounds exist predominantly in the tautomeric form of formula

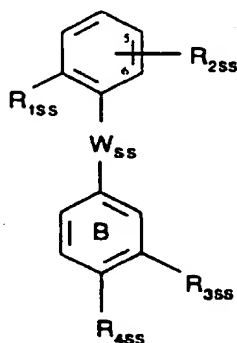


(I's)

wherein  $R'_{9s}$  is O or S,

in free form or, where such forms exist, in salt form.

An even further preferred group of compounds of the invention is the compounds of formula



(I'ss)

wherein

$R_{1ss}$  is hydroxy, alkyl of 1 or 2 carbon atoms or alkoxy of 1 or 2 carbon atoms;

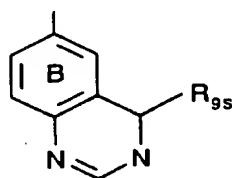
$R_{2ss}$  is hydroxy or alkoxy of 1 or 2 carbon atoms and is in the 5- or 6-position, whereby  $R_{1ss}$  and  $R_{2ss}$  are not simultaneously hydroxy;

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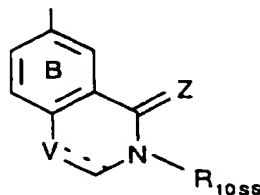
$W_{ss}$  is  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{NH}-$ ,  $-\text{CH}_2\text{O}-$  or  $-\text{CH}=\text{CH}-$ , whereby the nitrogen or oxygen atom is bound to ring B; and

$R_{3ss}$  and  $R_{4ss}$  together with ring B form a condensed ring system of formula



ass

or



bss

wherein

the symbol  $---$  is a single or a double bond;

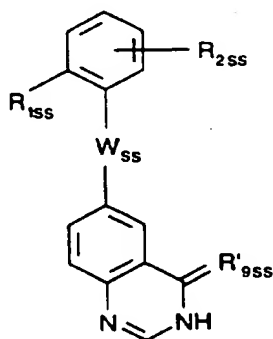
$R_{9s}$  is as defined above;

$R_{10ss}$  is hydrogen, methyl, 2,5-dimethoxybenzyl or 2,6-dimethoxybenzyl;

and

$Z$  and  $V$  are as defined above;

whereby, if  $R_{9s}$  is hydroxy or mercapto, then the compounds exist predominantly in the tautomeric form of formula



ltss

wherein  $R_{1ss}$  and  $R_{2ss}$  are as defined above and  $R'_{9ss}$  is oxygen or sulfur,

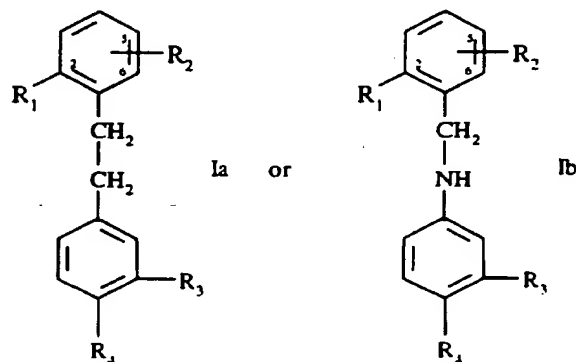
in free form or, where such forms exist, in salt form.

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In a subgroup of compounds of formula I ss  $R_{1ss}$  is methoxy or ethoxy. In a further subgroup thereof  $R_{2ss}$  is methoxy or ethoxy. In a further subgroup thereof  $W_{ss}$  is  $-\text{CH}_2\text{CH}_2-$ . In a further subgroup thereof  $R_{3ss}$  and  $R_{4ss}$  together with ring B form a condensed ring system of formula ass or bss wherein  $R_{9s}$  is alkyl or alkoxy, each of 1 to 4 carbon atoms;  $R_{10ss}$  is hydrogen, methyl or 2,5- or 2,6-dimethoxybenzyl; Z is O; and V is N and the symbol  $\equiv$  represents a double bond.

The present invention also provides processes for the preparation of compounds of formula I, comprising

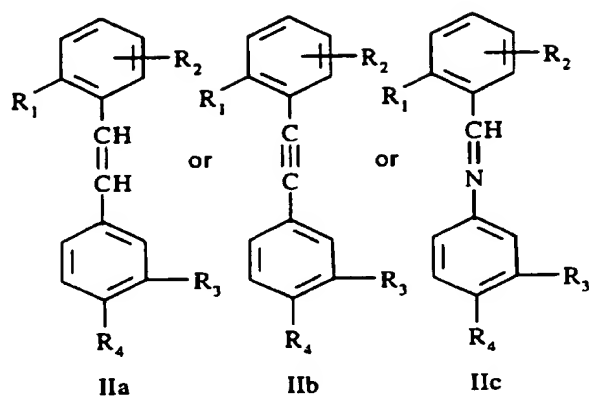
a) for the preparation of compounds of formula Ia and Ib



wherein the substituents are as defined above, reducing a compound of formula IIa, IIb or IIc

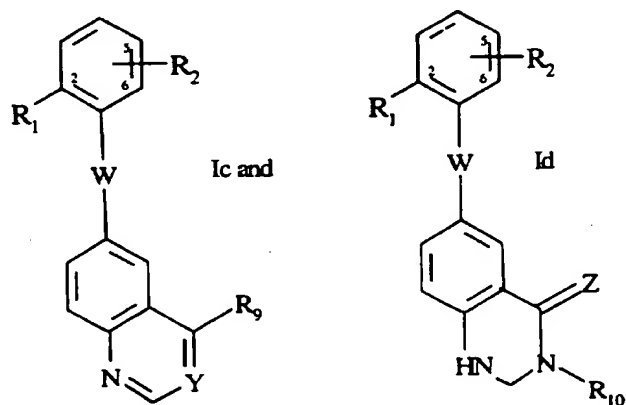
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wherein the substituents are as defined above, in conventional manner or

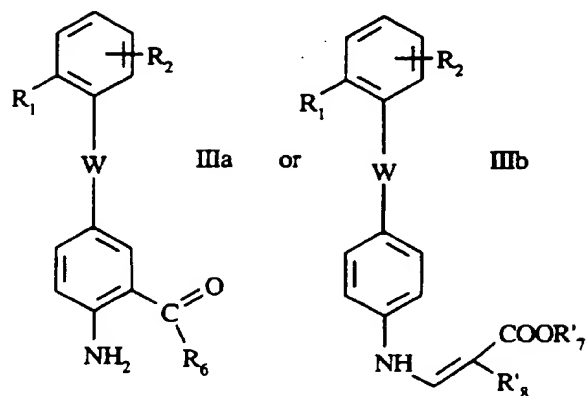
b) for the preparation of compounds of formula



wherein  $R_9$  is hydrogen, hydroxy or alkyl and the other substituents are as defined above, ring closure of the heterocycle of the bicyclic ring system starting from monocyclic precursors of formula

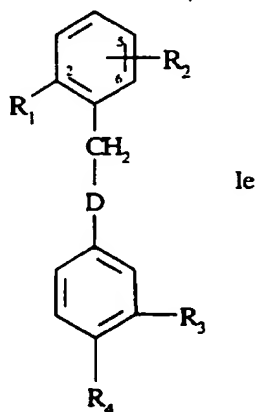
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wherein  $R'_7$  represents alkyl and  $R'_8$  represents alkoxy carbonyl, cyano or acyl, and the other substituents are as defined above, according to known methods for the preparation of quinolines and quinazolines, or

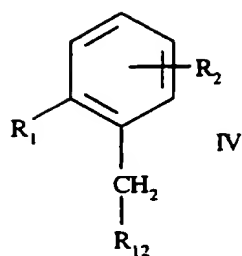
c) for producing compounds of formula



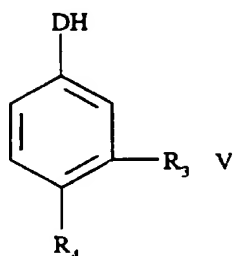
wherein the substituents are as defined above and D represents O or  $NR_5$ , reacting a compound of formula

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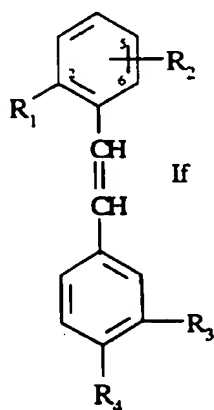


wherein  $R_{12}$  represents a leaving group, with a compound of formula



wherein the substituents are as defined above, or

d) for producing compounds of formula

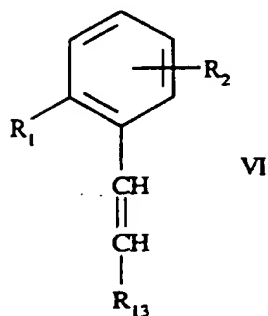


wherein the substituents are as defined above, coupling a compound of formula

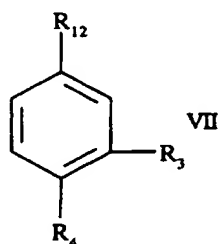
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wherein  $R_{13}$  represents a  $\text{Sn}(\text{alkyl})_3$ -group or a  $\text{B}(R_{14})_2$ -group, whereby  $R_{14}$  represents alkyl, cycloalkyl, alkoxy or aryloxy or the two substituents may form together with the boron atom a cyclic structure derived from 9-bora-bicyclononane or catecholborane, and the rest of the substituents are as defined above, with a compound of formula



wherein the substituents are as defined above, or

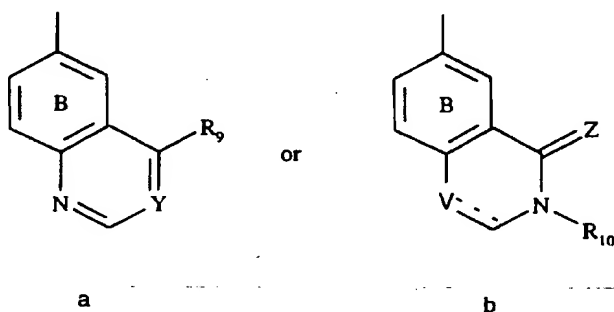
e) for the preparation of compounds of formula I starting from different compounds of formula I, by functional group transformation, such as ester, amide and ether cleavage, acylation and alkylation of hydroxy or amino functions, decarboxylation or by chemical manipulation of the heterocyclic ring system, such as reduction of or addition to  $-\text{C}=\text{N}-$  bonds,

whereby in these reactions functional groups may be protected by suitable protecting groups, which may be removed subsequent to the reaction in conventional manner, and recovering thus obtained compounds of formula I in free form or, where such forms exist, in salt form.

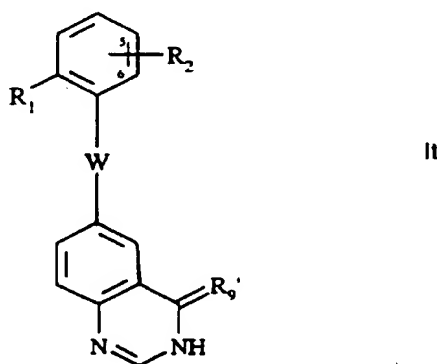
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b) W represents  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{O}-$  or  $-\text{CH}_2\text{NR}_5-$ , whereby the heteroatom adheres to ring B and  $\text{R}_5$  represents hydrogen, alkyl or acyl,  $\text{R}_3$  and  $\text{R}_4$  form together with the adjacent ring B a condensed ring system of formula



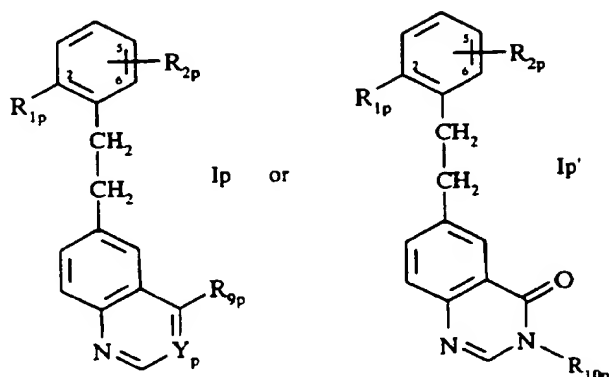
wherein the symbol  $\text{---}$  represents a single or a double bond,  $\text{R}_9$  represents hydrogen, alkylthio, alkyl, alkoxycarbonyl, acyl, amino, acylamino, diacylamino, alkylamino, dialkylamino, cyano, hydroxy, alkoxy or mercapto, Y represents N or  $\text{CR}_{11}$ ,  $\text{R}_{10}$  represents hydrogen, alkyl, acyl or optionally substituted phenylalkyl,  $\text{R}_{11}$  represents hydrogen, alkoxycarbonyl, cyano or acyl, Z represents O or S and V represents NH, if the symbol  $\text{---}$  represents a single bond, and N, if the symbol  $\text{---}$  represents a double bond, with the proviso that, if  $\text{R}_9$  represents hydroxy or mercapto and Y represents N, the compounds exist predominantly in the tautomeric form of formula



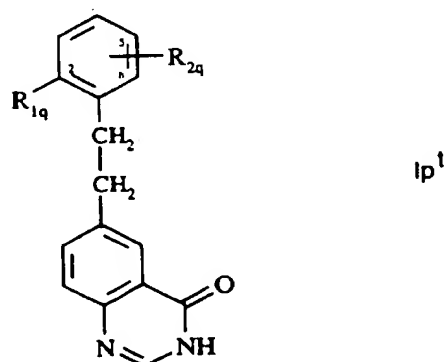
wherein  $\text{R}_9'$  represents O or S, in free form or, where such forms exist, in salt form.

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## 2. Compounds according to claim 1 of formula



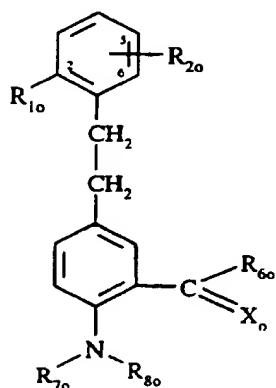
wherein  $R_{1p}$  and  $R_{2p}$  are the same or different and represent hydroxy, alkoxy, acyloxy, alkyl or acyl, whereby  $R_{2p}$  is in the 5- or 6-position, with the proviso that  $R_{1p}$  and  $R_{2p}$  are not simultaneously hydroxy or acyloxy,  $R_{9p}$  represents hydrogen, alkyl, alkoxycarbonyl, acyl, amino, acylamino, diacylamino, alkylamino, dialkylamino, cyano, alkoxy or hydroxy,  $Y_p$  represents N or CH and  $R_{10p}$  represents hydrogen, alkyl or acyl, with the proviso that, if  $R_{9p}$  represents hydroxy and  $Y_p$  represents N, the compounds exist predominantly in the tautomeric form of formula



in free form, or where such forms exist, in salt form.

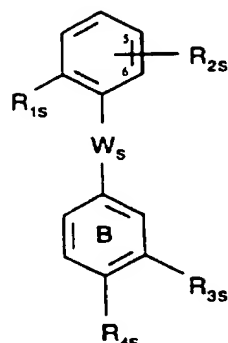
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## 3. Compounds according to claim 1 of formula



wherein  $R_{10}$  and  $R_{20}$  are the same or different and represent alkyl, acyl or alkoxy, and  $R_{60}$ ,  $R_{70}$ ,  $R_{80}$  and  $X_0$  have the same significance as  $R_6$ ,  $R_7$ ,  $R_8$  and  $X$  as defined in claim 1, in free form or, where such forms exist, in salt form.

## 4. Compounds according to claim 1 of formula



Is

wherein

$R_{1s}$  is hydroxy, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

$R_{2s}$  is hydroxy or alkoxy of 1 to 4 carbon atoms and is in the 5- or 6-position, whereby  $R_{1s}$  and  $R_{2s}$  are not simultaneously hydroxy; and

a)  $W_s$  is  $-CH_2CH_2-$ ;

$R_{3s}$  is a group of formula  $-COR_{6s}$  wherein

$R_{6s}$  is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or amino; and

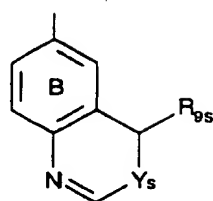
$R_{4s}$  is amino, alkylamino of 1 to 4 carbon atoms, dialkylamino independently of 1 to 4 carbon atoms in each alkyl part thereof, alkylcarbonylamino of 1 to 4 carbon atoms in the alkyl part thereof, or alkoxycarbonylamino of 1 to 4 carbon atoms in the alkoxy part thereof; or

b)  $W_s$  is  $-CH_2CH_2-$ ,  $-CH_2NH-$ ,  $-CH_2O-$  or  $-CH=CH-$ , whereby the nitrogen or oxygen atom is bound to ring B; and

$R_{3s}$  and  $R_{4s}$  together with ring B form a condensed ring system of formula

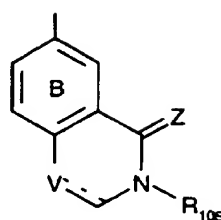
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as

or



bs

wherein

the symbol  $\text{---}$  is a single or a double bond;

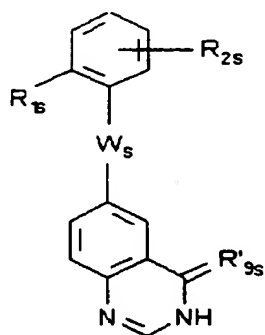
$R_{9s}$  is hydrogen, alkylthio of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms, amino, diacetyl amino, alkyl amino of 1 to 4 carbon atoms, hydroxy, alkoxy of 1 to 4 carbon atoms or mercapto;

$Y_s$  is N or  $CR_{11s}$ , wherein  $R_{11s}$  is hydrogen or alkoxycarbonyl of 1 to 4 carbon atoms in the alkoxy part thereof,

$R_{10s}$  is hydrogen, alkyl of 1 to 4 carbon atoms or dialkoxybenzyl independently of 1 to 4 carbon atoms in the alkoxy parts thereof; and

Z and V are as defined in claim 1;

with the proviso that, if  $R_{9s}$  is hydroxy or mercapto and  $Y_s$  is N, then the compounds exist predominantly in the tautomeric form of formula



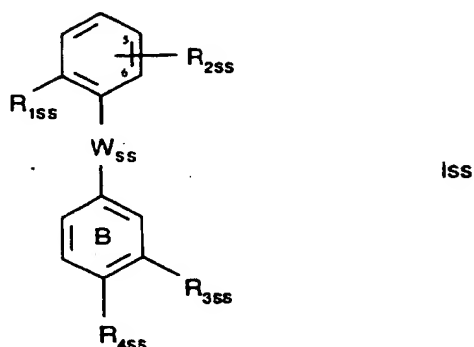
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wherein  $R'_{9s}$  is O or S,

in free form or, where such forms exist, in salt form.

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5. Compounds according to claim 1 of formula

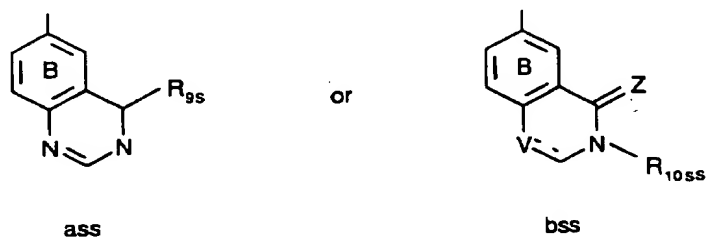


wherein

$R_{1ss}$  is hydroxy, alkyl of 1 or 2 carbon atoms or alkoxy of 1 or 2 carbon atoms;  
 $R_{2ss}$  is hydroxy or alkoxy of 1 or 2 carbon atoms and is in the 5- or 6-position,  
 whereby  $R_{1ss}$  and  $R_{2ss}$  are not simultaneously hydroxy;

$W_{ss}$  is  $-CH_2CH_2-$ ,  $-CH_2NH-$ ,  $-CH_2O-$  or  $-CH=CH-$ , whereby the nitrogen or oxygen atom is bound to ring B; and

$R_{3ss}$  and  $R_{4ss}$  together with ring B form a condensed ring system of formula



wherein

the symbol  $\equiv$  is a single or a double bond;

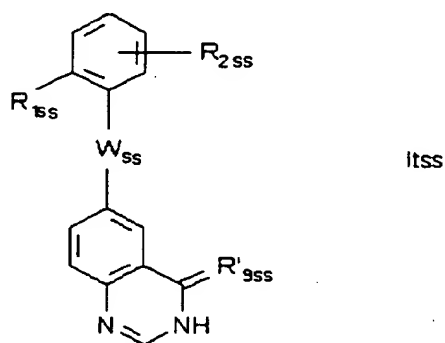
$R_{9s}$  is as defined in claim 4;

$R_{10ss}$  is hydrogen, methyl, 2,5-dimethoxybenzyl or 2,6-dimethoxybenzyl; and

Z and V are as defined in claim 1;

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whereby, if  $R_{9s}$  is hydroxy or mercapto, then the compounds exist predominantly in the tautomeric form of formula



wherein  $R_{1ss}$  and  $R_{2ss}$  are as defined in this claim and  $R'_{9ss}$  is oxygen or sulfur,  
in free form or, where such forms exist, in salt form.

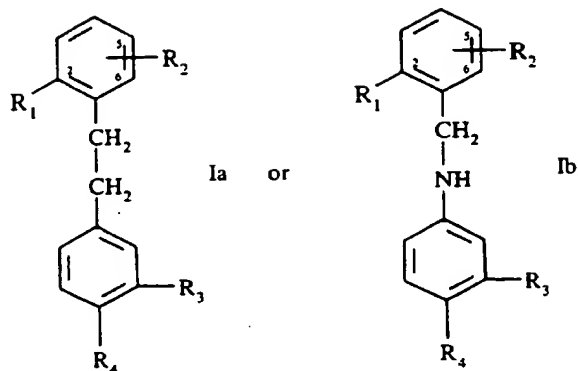
6. The compound 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-ethyl-quinazoline, or 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-ethoxy-quinazoline, or 6-[2-(2,5-dimethoxyphenyl)ethyl]-4-methyl-quinazoline, in free form or, where such forms exist, in salt form.

7. Process for the preparation of compounds of formula I as defined in claim 1, comprising

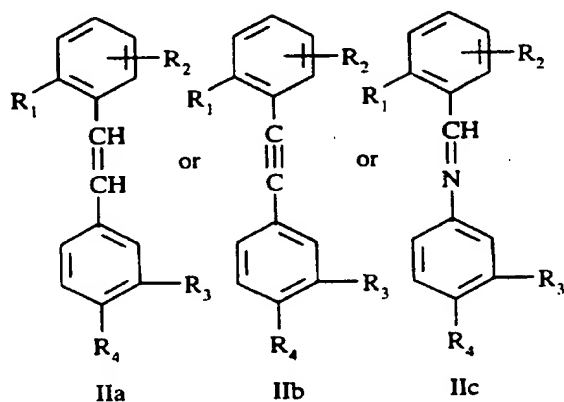
a) for the preparation of compounds of formula Ia and Ib



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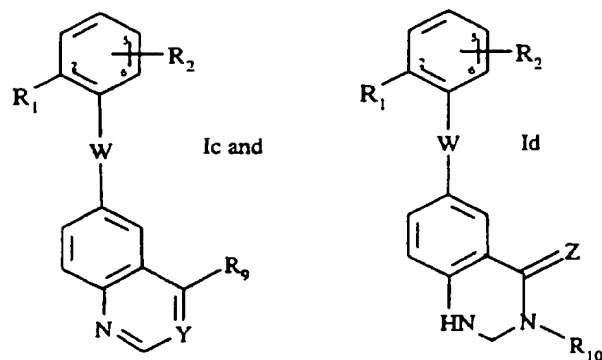
wherein the substituents are as defined in claim 1, reducing a compound of formula IIa, IIb or IIc



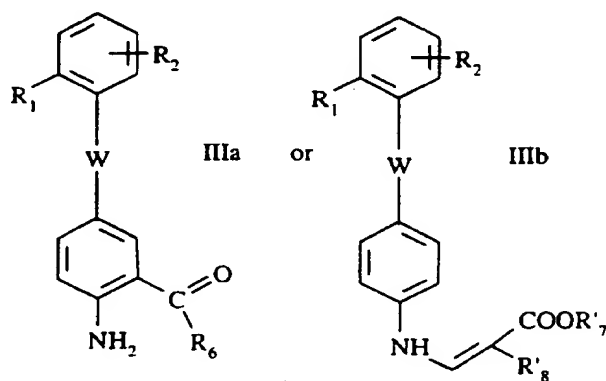
wherein the substituents are as defined in claim 1, in conventional manner or

b) for the preparation of compounds of formula

**SUBSTITUTE SHEET (RULE 26)**



wherein  $R_9$  is hydrogen, hydroxy or alkyl and the other substituents are as defined in claim 1, ring closure of the heterocycle of the bicyclic ring system starting from monocyclic precursors of formula

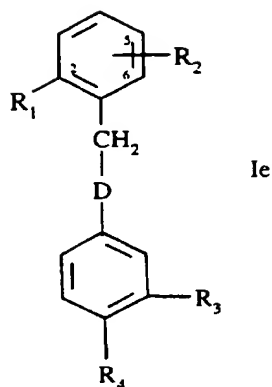


wherein  $R'_7$  represents alkyl,  $R'_8$  represents alkoxy carbonyl, cyano or acyl and  $R_1$ ,  $R_2$  and  $R_6$  are as defined in claim 1, according to known methods for the preparation of quinolines and quinazolines, or

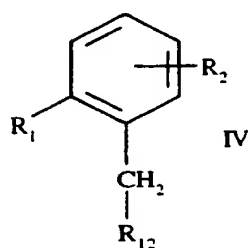
c) for producing compounds of formula

**SUBSTITUTE SHEET (RULE 26)**

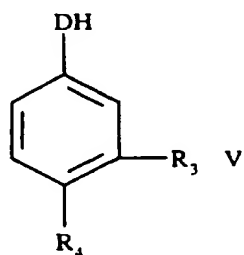
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wherein the substituents are as defined in claim 1 and D represents O or NR<sub>5</sub>  
 wherein R<sub>5</sub> is as defined in claim 1, reacting a compound of formula



wherein R<sub>12</sub> represents a leaving group, with a compound of formula

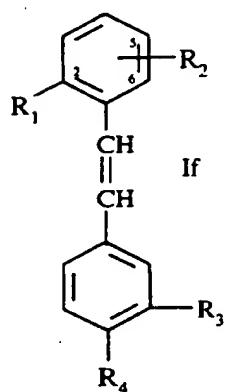


wherein the substituents are as defined in claim 1, or

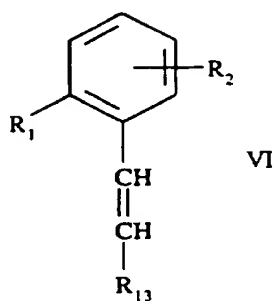
d) for producing compounds of formula

**SUBSTITUTE SHEET (RULE 26)**

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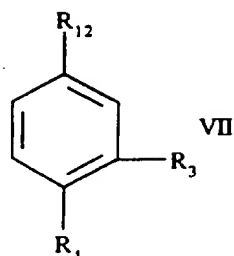
wherein the substituents are as defined in claim 1, coupling a compound of formula



wherein  $R_{13}$  represents a  $\text{Sn}(\text{alkyl})_3$ -group or a  $\text{B}(\text{R}_{14})_2$ -group, whereby  $\text{R}_{14}$  represents alkyl, cycloalkyl, alkoxy or aryloxy or the two substituents may form together with the boron atom a cyclic structure derived from 9-bora-bicyclononane or catecholborane, and  $\text{R}_1$  and  $\text{R}_2$  are as defined in claim 1, with a compound of formula

**SUBSTITUTE SHEET (RULE 26)**

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wherein R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1 and R<sub>12</sub> is as defined in this claim, or

e) for the preparation of compounds of formula I starting from different compounds of formula I, by functional group transformation, such as ester, amide and ether cleavage, acylation and alkylation of hydroxy or amino functions, decarboxylation or by chemical manipulation of the heterocyclic ring system, such as reduction of or addition to -C=N- bonds,

whereby in these reactions functional groups may be protected by suitable protecting groups, which may be removed subsequent to the reaction in conventional manner, and recovering thus obtained compounds of formula I in free form or, where such forms exist, in salt form.

8. A pharmaceutical composition comprising a compound according to claim 1 to 6 together with at least one pharmaceutically acceptable carrier or diluent.

9. A process for the preparation of a pharmaceutical composition according to claim 8 comprising mixing a compound according to claim 1 to 6 together with at least one pharmaceutically acceptable carrier or diluent.

10. A compound according to claim 1 to 6 for use as a pharmaceutical.

11. A compound according to claim 1 to 6 for use in the prevention or treatment of inflammatory and proliferative skin diseases or cancer.

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12. A method of prevention or treatment of inflammatory and proliferative skin diseases or cancer, comprising administering a therapeutically effective amount of a compound according to claim 1 to 6 to a subject in need of such treatment.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/01116

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D239/88 C07D239/74 C07D239/94 C07C229/56 C07C237/30  
C07D215/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 497 740 (SANDOZ) 5 August 1992 see page 1 - page 8; claims; examples 15,16 -----	1-3,7-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

18 June 1996

Date of mailing of the international search report

25.06.96

Name and mailing address of the ISA

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Authorized officer

Francois, J

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/01116

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 12 is directed to a method of treatment of the human body, the search has been carried out and based on the attributed effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/01116

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-497740	05-08-92	AT-T- 115541	15-12-94
		AU-B- 1058492	06-08-92
		CA-A- 2060352	02-08-92
		DE-D- 69200863	26-01-95
		JP-A- 5070400	23-03-93
		NZ-A- 241467	25-02-94
		ZA-A- 9200721	02-08-93
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/02606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9515758	15-06-95	US-A- 5480883 AU-B- 1305095	02-01-96 27-06-95

Form PCT/ISA/210 (patent family sheet) (July 1992)

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